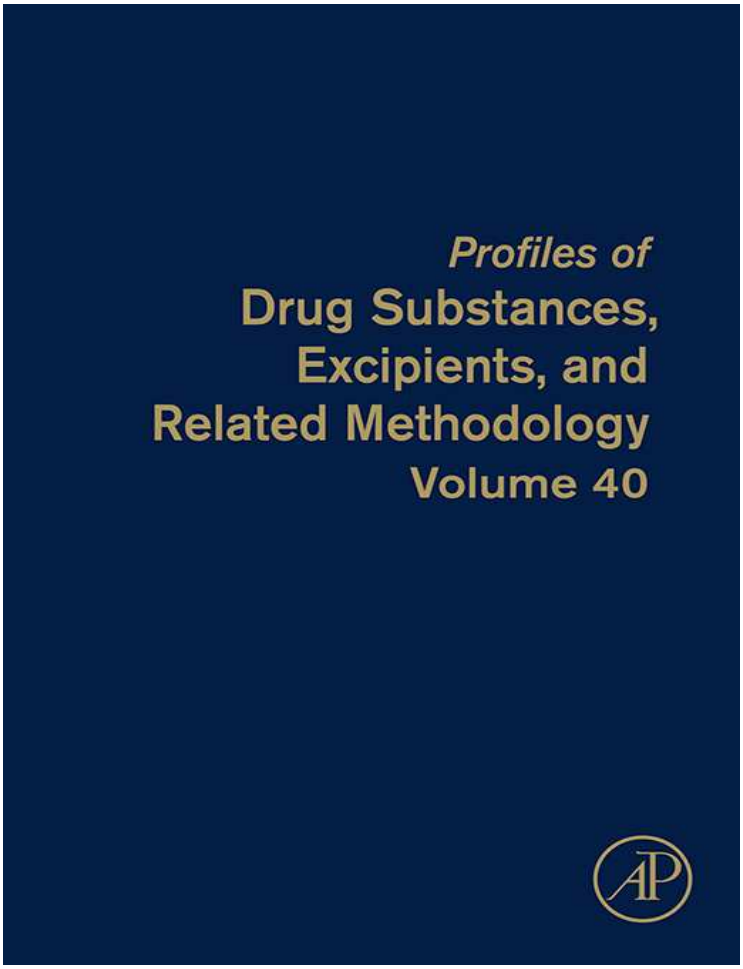

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CHAPTER ONE

Cinnarizine: Comprehensive Profile

Nadia G. Haress[1]
Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[1]Corresponding author: e-mail address: nharess@ksu.edu.sa; nadiaharess@hotmail.com

Contents

1. DESCRIPTION

1.1 Nomenclature

1.1.1 Systemic Chemical Names

- 1-(Diphenylmethyl)-4-(3-phenyl-2-propenyl)piperazine
- 1-Cinnamyl-4-diphenylmethylpiperazine

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- *N*-Benzhydryl-*N*-*trans*-cinnamylpiperazine
- 1-*trans*-Cinnamyl-4-diphenylmethylpiperazine
- 1-Cinnamyl-4-benzhydrylpiperazine
- 1-Diphenylmethyl-4-*trans*-cinnamylpiperazine [1–4]

1.1.2 Nonproprietary Names

Cinnarizine, cinnarizin [1–4]

1.1.3 Proprietary Names

1.1.3.1 Cinnarizine

Cinniprine®, 516-MD®, Aplactan®, Aplexal®, Apotomin®, Artate®, Carecin®, Cerebolan®, Cerepar®, Cinnaperazine®, Cinazyn®, Cinnacet®, Cinnageron®, Corathiem®, Denapol®, Dimitron®, Eglen®, Folcodal®, Giganten®, Glanil®, Hilactan®, Ixertol®, Katoseran®, Labyrin®, Midronal®, Mitronal®, Olamin®, Processine®, Sedatromin®, Sepan®, Siptazin®, Spaderizine®, Stugeron®, Stutgin®, Toliman® [1–4].

1.1.3.2 Cinnarizine Hydrochloride

Linazine®, Siarizine®, Silicin®, Sorebral®.

1.1.3.3 Mixture with Vitamin B_6

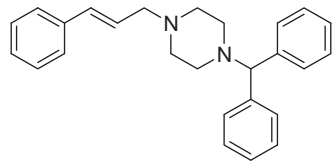
Emasazine®, C-Sik®

1.2 Formulae

1.2.1 Empirical Formula, Molecular Weight, and CAS Number

Cinnarizine	$C_{26}H_{28}N_2$	368.51	298-57-7
Cinnarizine hydrochloride	$C_{26}H_{28}N_2 \cdot HCl$	404.97	700-58-6

1.2.2 Structural Formulae



1.3 Elemental Analysis

Cinnarizine	C, 84.74%	H, 7.66%	N, 7.60%	
Cinnarizine hydrochloride	C, 77.11%	H, 7.22%	N, 6.92%	Cl, 8.75% [1]

1.4 Appearance

Cinnarizine is a white or almost white powder [1–3].

1.5 Uses and Applications

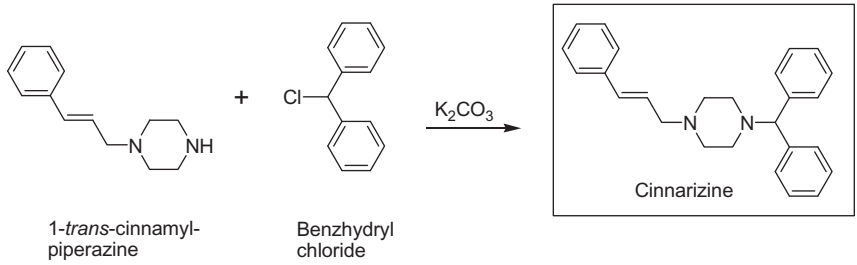
Cinnarizine is a piperazine derivative with antihistaminic, antiserotonergic, antidopaminergic, and calcium channel-blocking activities. It is currently used for the treatment of nausea, vomiting, and vertigo caused by Meniere's disease and other vestibular disorders. Cinnarizine is also used for prevention and treatment of motion sickness. It is also widely used for the treatment of cerebral thrombosis, cerebral embolism, cerebral arteriosclerosis, and diseases caused by poor peripheral circulation [3]. It is also reported that cinnarizine is effective in the treatment of some allergic diseases, such as chronic urticaria and senile skin pruritus [3].

Cinnarizine is given orally as tablets or capsules which may result in a very slow bioavailability and a wide individual variation [3,4].

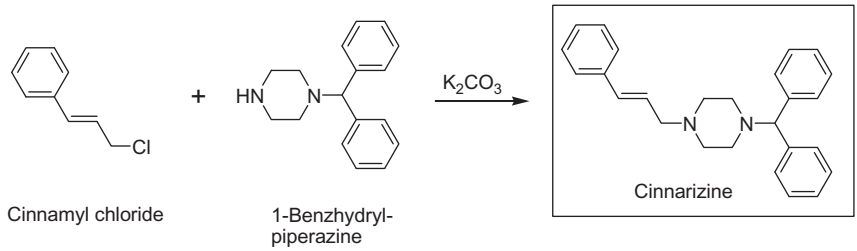
Intravenous cinnarizine administration is an alternative to oral administration which provides greater bioavailability, faster therapeutic effect, and lower individual difference than oral dosing. However, any injectable dosage forms can cause pain at the injection site, venous irritation, and possible precipitation of the drug after intravenous administration resulting in restriction of their clinical applications and industrial-scale production [3,4].

2. METHODS OF PREPARATION

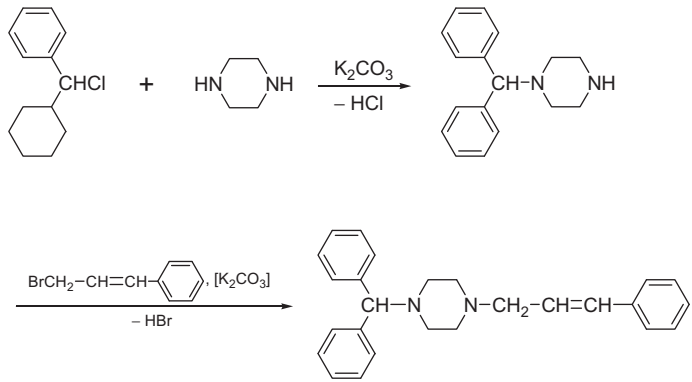
Cinnarizine was prepared by Janssen Pharmaceutical Companies [5] by two methods. The first one was achieved by reacting 1-*trans*-cinnamylpiperazine with benzhydryl chloride in an alkaline medium (Scheme 1), while the other method was performed by the addition of cinnamyl chloride to 1-benzylpiperazine in the presence of sodium carbonate (Scheme 2).



Scheme 1 Synthesis of cinnarizine by Janssen Pharmaceutical Companies (first method).



Scheme 2 Synthesis of cinnarizine by Janssen Pharmaceutical Companies (second method).



Scheme 3 Synthesis of cinnarizine by a reported method.

Cinnarizine was also prepared by the reaction of piperazine with benzhydryl chloride, followed by N-alkylation with cinnamyl bromide or chloride (Scheme 3) [6].

In addition, Sheng *et al.* [7] reported a convenient synthesis of cinnarizine by Mannich reaction of 1-benzhydrylpiperazine with HCHO and

PhCOMe, followed by the reduction of the resultant propiophenone derivative and subsequent dehydration of the alcohol to afford cinnarizine in quantitative yield.

3. PHYSICAL CHARACTERISTICS

3.1 Ionization Constant

$pK_a = 7.8$
Log $P = 6.14$ [8]

3.2 Solubility Characteristics

Cinnarizine: Practically insoluble in water. Slightly soluble in ethanol (96%) and methanol. Soluble in acetone and freely soluble in dichloromethane. Protect from light [1–3].
Cinnarizine hydrochloride: Soluble 2 mg/100 mL in water [1–3].

3.3 X-Ray Powder Diffraction Pattern

The X-ray powder diffraction pattern of cinnarizine was performed using a Bruker-Nonius FR590 diffractometer. Figure 1 shows the X-ray powder diffraction pattern of cinnarizine, which was obtained on a pure sample of the drug substance. Table 1 shows the values for the scattering angles

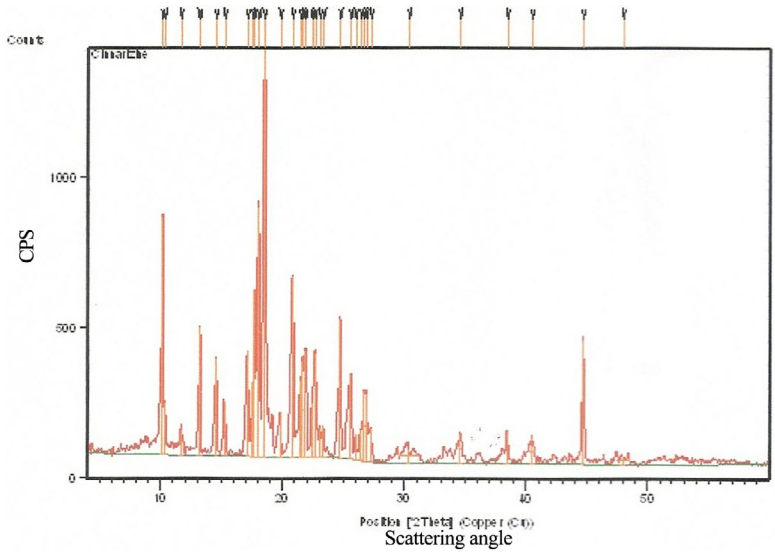


Figure 1 The X-ray diffraction pattern of cinnarizine.

Table 1 The X-Ray Powder Diffraction Pattern of Cinnarizine

Position (°2θ)	Height (cts)	FWHM Left (°2θ)	d-Spacing (Å)	Relative Intensity (%)
10.1300	789.24	0.0900	8.72502	57.95
10.3243	173.35	0.0900	8.56133	12.73
11.6712	88.89	0.3070	7.58239	6.53
13.1005	232.89	0.0900	6.75258	17.10
13.2245	427.43	0.0768	6.69508	31.39
14.5404	323.93	0.1279	6.09200	23.79
15.2189	181.93	0.2047	5.82191	13.36
17.0963	353.10	0.0900	5.18230	25.93
17.5123	247.33	0.0900	5.06013	18.16
17.6765	554.26	0.0768	5.01763	40.40
18.0114	826.60	0.0900	4.92100	60.70
18.4553	1361.85	0.0900	4.80365	100.00
19.7652	152.87	0.1535	4.49186	11.23
20.7696	603.13	0.0900	4.27330	44.29
21.4551	254.51	0.0900	4.13831	18.69
21.6264	319.60	0.0900	4.10590	23.47
21.8549	352.73	0.0900	4.06349	25.90
22.3690	179.01	0.0900	3.97126	13.14
22.5974	345.14	0.0900	3.93162	25.34
23.0258	101.38	0.0900	3.85943	7.44
23.3257	110.54	0.0900	3.81049	8.12
24.6931	459.60	0.0900	3.60249	33.75
25.5281	285.59	0.0900	3.48652	20.97
25.9534	86.62	0.0900	3.43033	6.36
26.3946	105.73	0.0900	3.37400	7.76
26.6781	233.08	0.0900	3.33877	17.12
27.1980	116.57	0.0900	3.27612	8.56
30.3314	51.89	1.6374	2.94688	3.81

Table 1 The X-Ray Powder Diffraction Pattern of Cinnarizine—cont'd

Position (°2θ)	Height (cts)	FWHM Left (°2θ)	d-Spacing (Å)	Relative Intensity (%)
34.5428	96.91	0.3070	2.59664	7.12
40.4625	83.29	0.4093	2.22937	6.12
44.6465	414.33	0.2047	2.02968	30.42
47.9395	27.19	1.2280	1.89767	2.00

(deg, 2θ), the interplanar d-spacing (Å), and the relative intensities (%) observed for the major diffraction peaks of cinnarizine.

3.4 Thermal Method of Analysis

3.4.1 Melting Behavior

Cinnarizine melts at 118–122 °C.

Cinnarizine hydrochloride melts at 192 °C [1].

3.5 Spectroscopy

3.5.1 Ultraviolet Spectroscopy

The UV absorption spectrum of cinnarizine in 0.1 N hydrochloric acid shown in Figure 2 was recorded using an Ultrospec 2100 pro UV/Vis Spectrophotometer. Compound exhibited a maximum at 253 nm (A 1%, 1 cm = 584). Clarke reported the following: aqueous acid—254 nm (A 1%, 1 cm = 584) [2].

3.5.2 Vibrational Spectroscopy

The infrared absorption spectrum of cinnarizine was obtained as KBr disc using a Jasco FT/IR-4100 infrared spectrophotometer. The infrared spectrum is shown in Figure 3, where the principle peaks are observed at 3064, 3021, 2953, 2873, 1134, 997, and 965 cm^{-1}. Assignment for the major infrared absorption bands is shown in Table 2.

Clarke reported principle peaks at 702, 691, 1138, 964, 740, and 1000 cm^{-1} (KBr disc) [2].

3.5.3 Nuclear Magnetic Resonance Spectrometry

3.5.3.1 ^{1}H NMR Spectrum

The proton NMR spectrum of cinnarizine was obtained using a Bruker instrument operating at 500 MHz. Standard Bruker software was used to execute the recording of DEPT, COSY, and HETCOR spectra. The

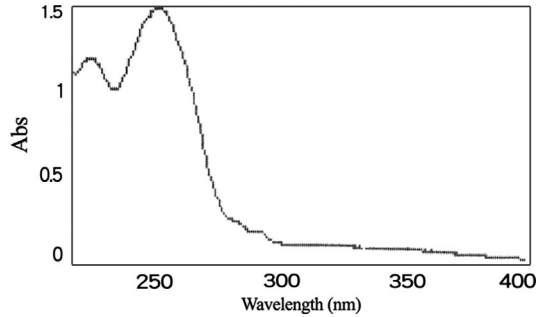


Figure 2 The UV absorption spectrum of cinnarizine.

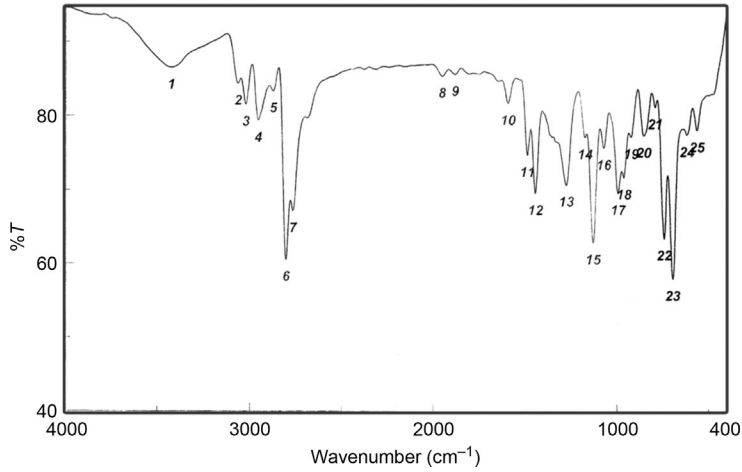


Figure 3 The infrared absorption spectrum of cinnarizine (KBr disc).

Table 2 $\pm R$ (ν, cm^{-1}) Assignments of Cinnarizine

Frequency (cm^{-1})	Assignments
3064, 3021	CH stretching (aromatic and alkene)
2953, 2873	CH stretch (aliphatic)
1134	C—N stretching
997, 965	=C—H out of plane (oop) (alkene and Aromatic)

sample was dissolved in DMSO-d_6 and all resonance bands were referenced to tetramethylsilane (TMS) as internal standard. The ^{1}H NMR spectra of cinnarizine are shown in Figures 4–6 and the COSY ^{1}H NMR spectrum is shown in Figures 7 and 8. The ^{1}H NMR assignments for cinnarizine are provided in Table 3.

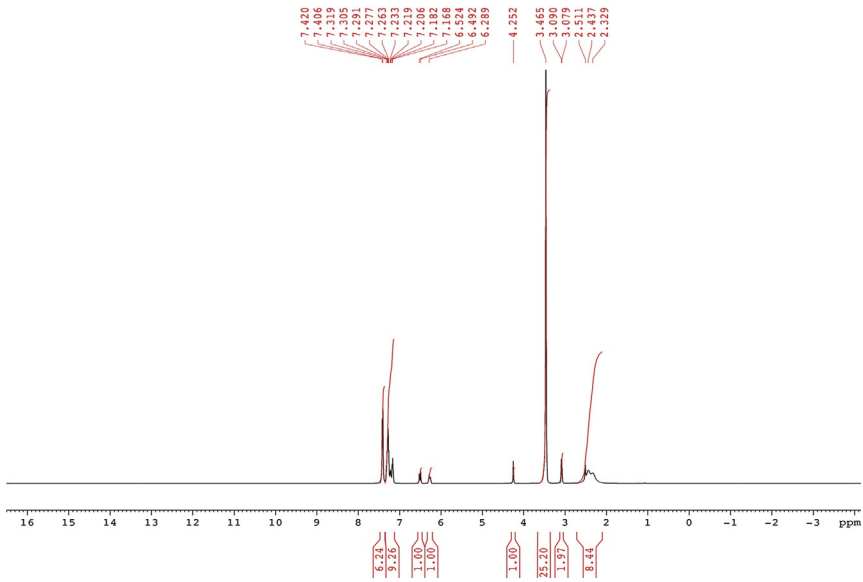


Figure 4 ^{1}H NMR spectrum of cinnarizine.

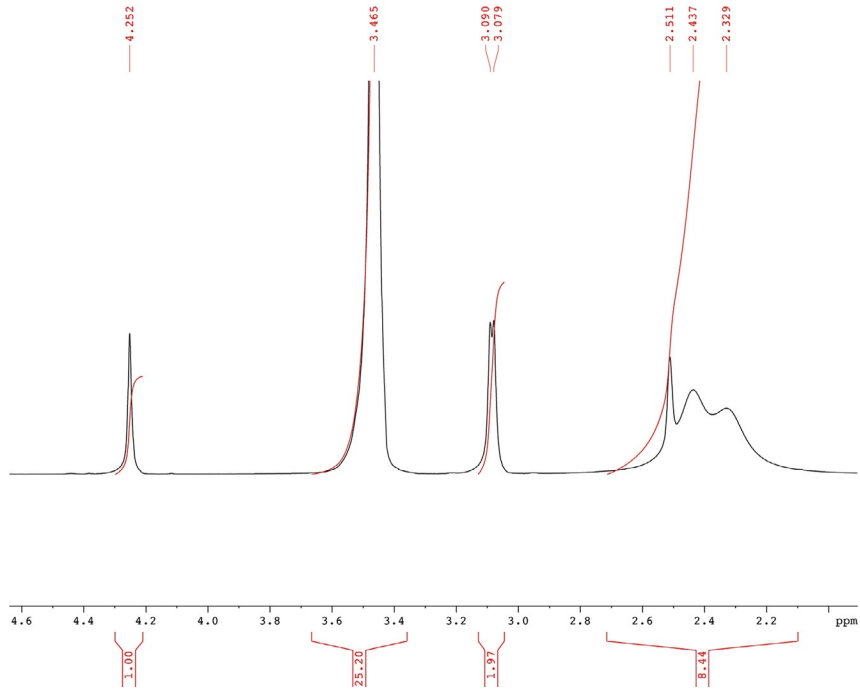


Figure 5 Partial expanded ^{1}H NMR spectrum (δ 2.1–4.6 ppm) of cinnarizine.

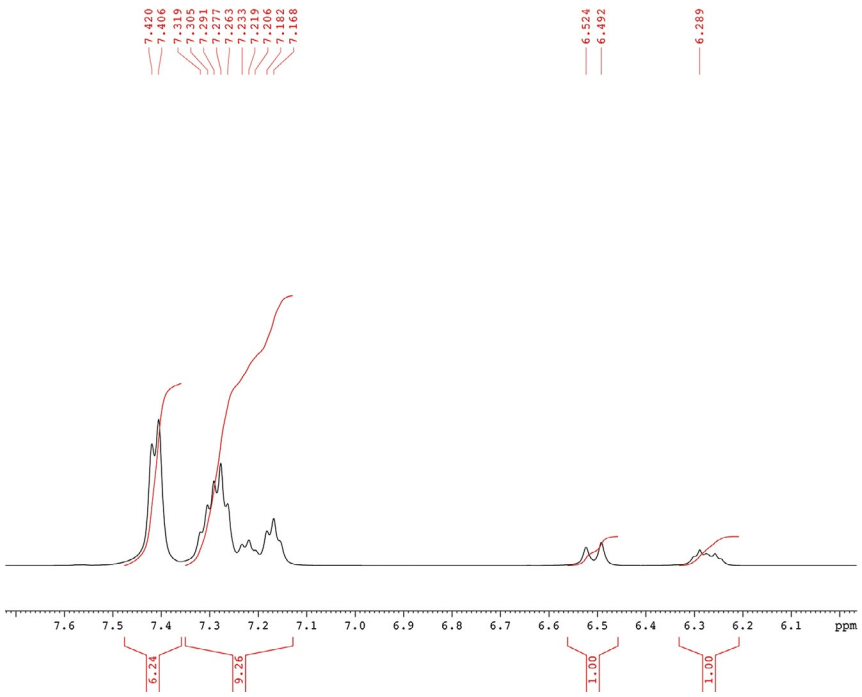


Figure 6 Partial expanded ^{1}H NMR spectrum (δ 6.2–7.5 ppm) of cinnarizine.

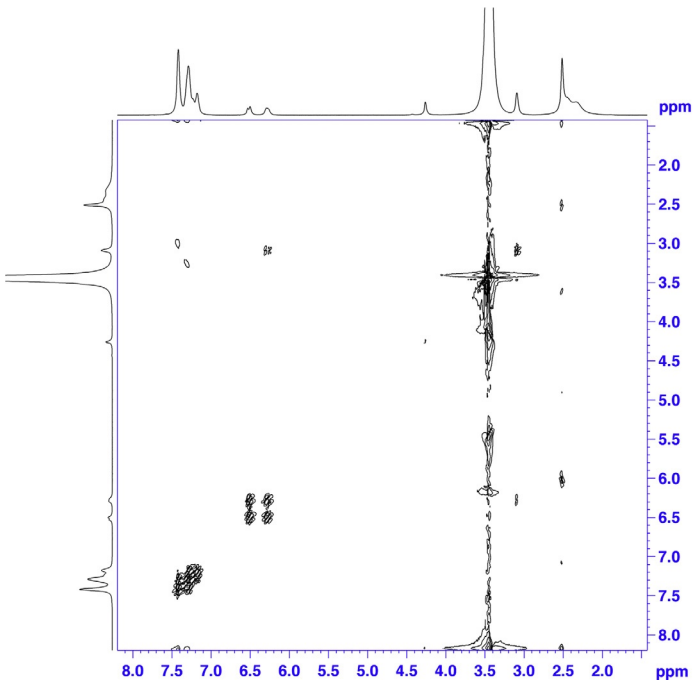


Figure 7 COSY-1 ^{1}H NMR spectrum of cinnarizine in DMSO-d_6.

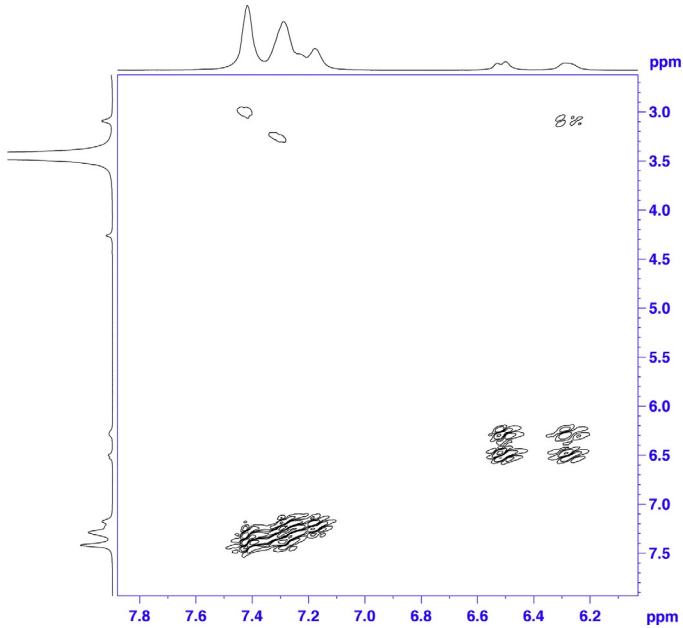


Figure 8 COSY-2 ^{1}H NMR spectrum of cinnarizine.

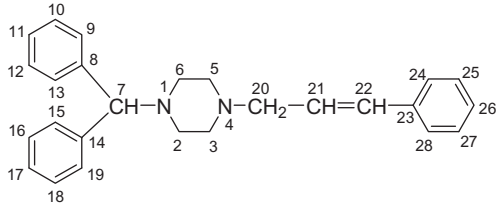
3.5.3.2 ^{13}C NMR Spectrum

The carbon-13 NMR spectra of cinnarizine were obtained using a Bruker instrument operating at 125 MHz. The sample was dissolved in DMSO-d_6 and TMS was added to function as the internal standard. The ^{13}C NMR spectra are shown in Figures 9 and 10 and the HSQC and HMBC NMR spectra were shown in Figures 11–15, respectively. The DEPT 90 and DEPT 135 are shown in Figures 16–19, respectively. The assignments for the observed resonance bands associated with the various carbons are listed in Table 4. Summary of assignments for the nuclear magnetic resonance bands of cinnarizine is shown in Table 5.

3.5.4 Electron Impact Mass Spectrometry

The electron impact (EI) mass spectrum of cinnarizine was obtained using a Shimadzu QP-2010 plus mass spectrometer. Figure 20 shows the detailed mass fragmentation pattern for cinnarizine. Table 6 shows the proposed mass fragmentation pattern of the drug.

Table 3 [1]H NMR (δ ppm) Assignments of the Resonance Bands in Cinnarizine



Chemical Shift (δ ppm, Relative to TMS)	Number of Protons	Multiplicity[a]	Assignments
2.33	4	m	H-2 and H-6
2.44	4	m	H-3 and H-5
3.08	2	d	H-20
4.25	1	s	H-7
6.29	1	m	H-21
6.51	1	d	H-22
7.17–7.18	2	m	H-11 and H-17
7.21	1	m	H-26
7.22–7.29	6	m	H-9, H-13, H-15, H-19, H-25, and H-27
7.31–7.42	6	m	H-10, H-12, H-16, H-18, H-24, and H-28

[a]s, singlet; d, doublet; m, multiplet.

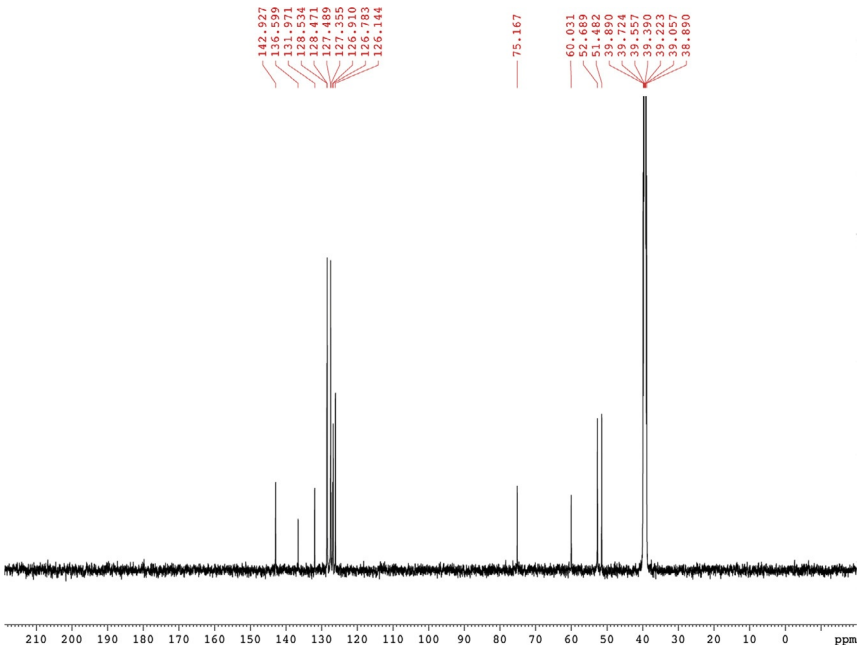


Figure 9 [13]C NMR spectrum of cinnarizine in DMSO-d_6.

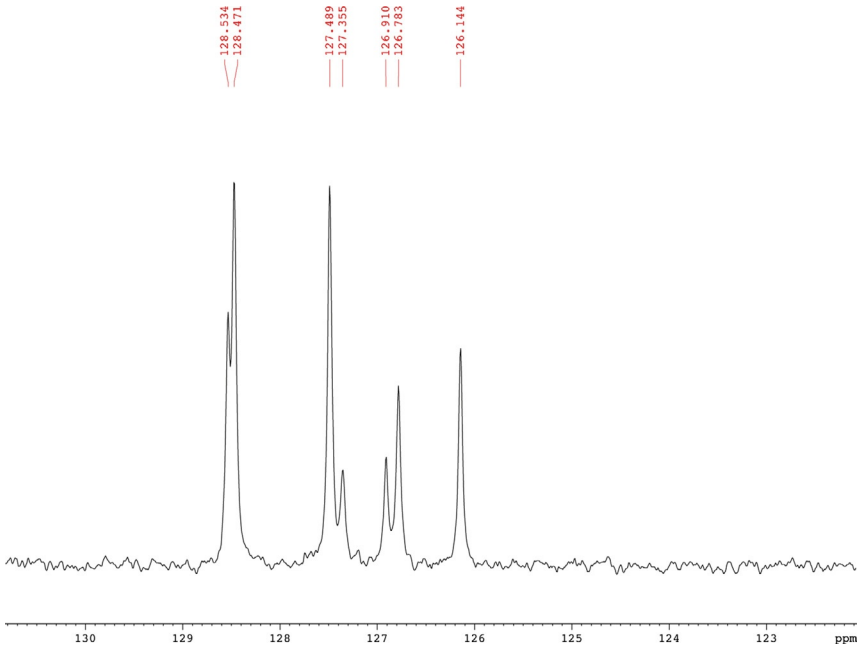


Figure 10 Expanded ^{13}C NMR spectrum of cinnarizine in DMSO-d_6.

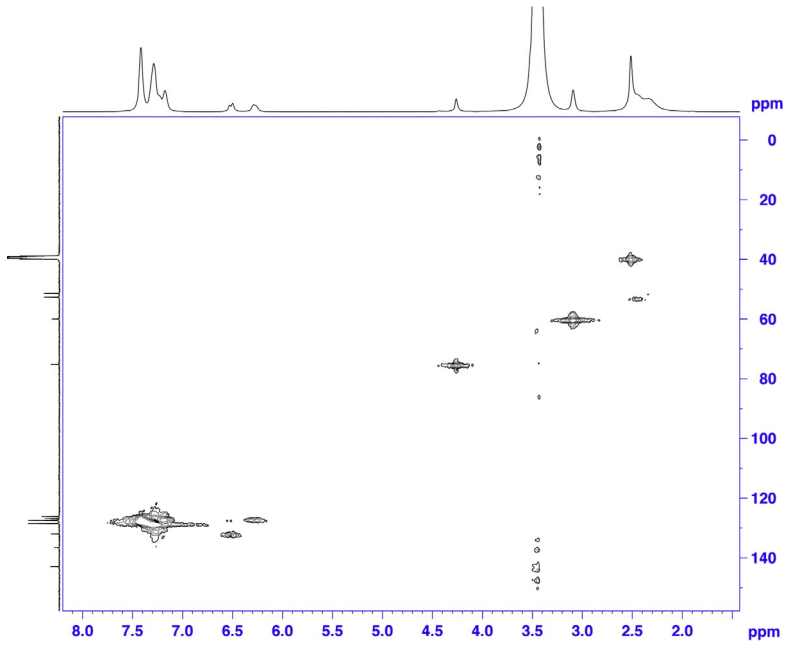


Figure 11 The HMQC-1 spectrum of cinnarizine in DMSO-d_6.

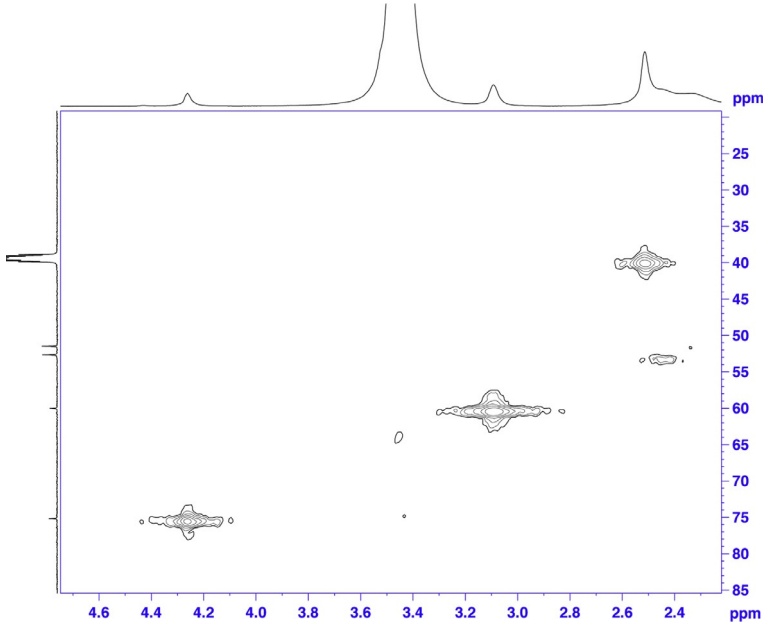


Figure 12 The HMQC-2 spectrum of cinnarizine in DMSO-d_6.

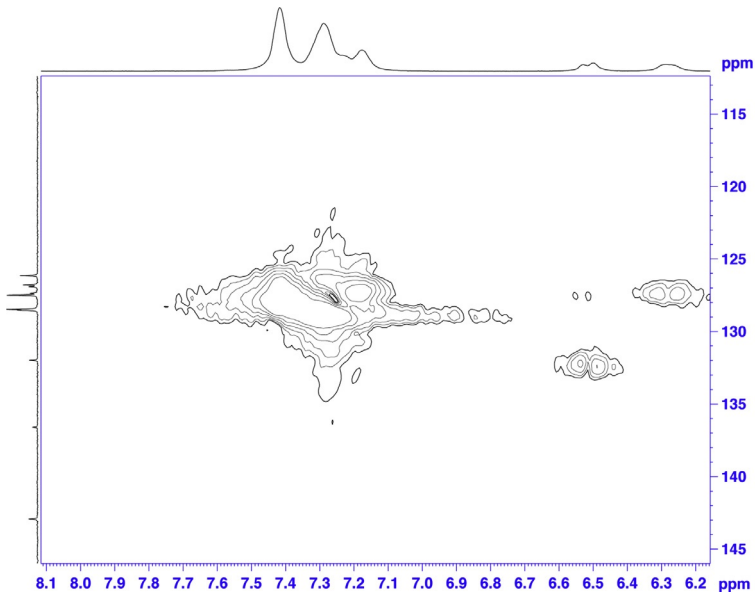


Figure 13 The HMQC-3 spectrum of cinnarizine in DMSO-d_6.

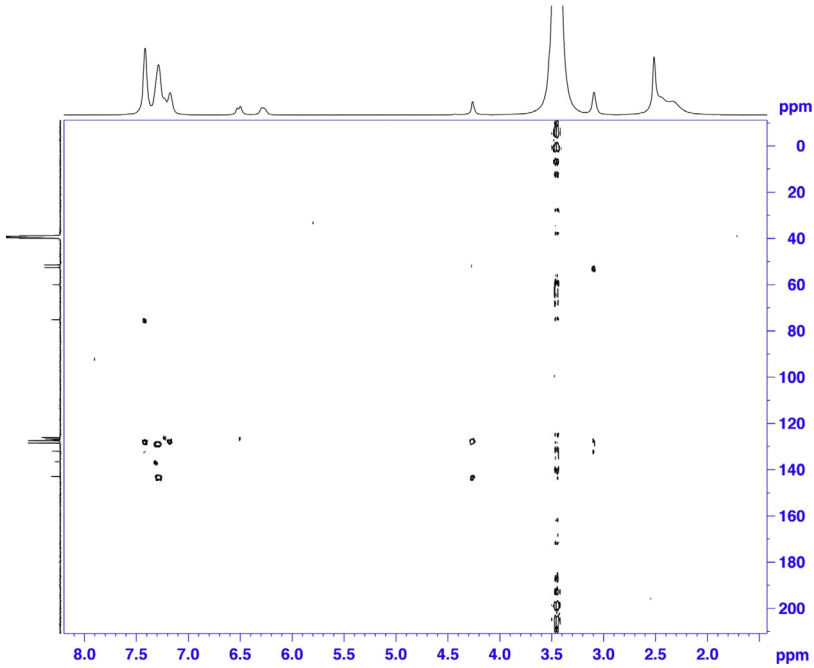


Figure 14 The HMBC-1 spectrum of cinnarizine in DMSO-d_6.

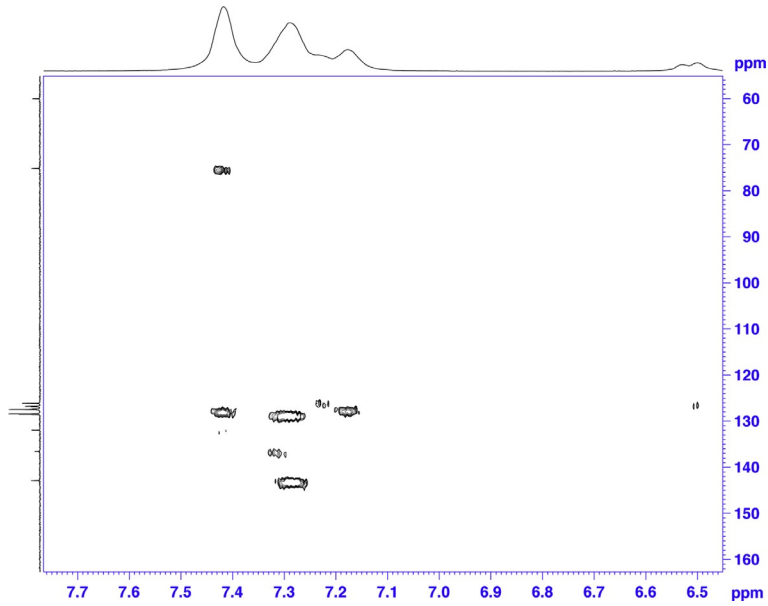


Figure 15 The HMBC-2 spectrum of cinnarizine in DMSO-d_6.

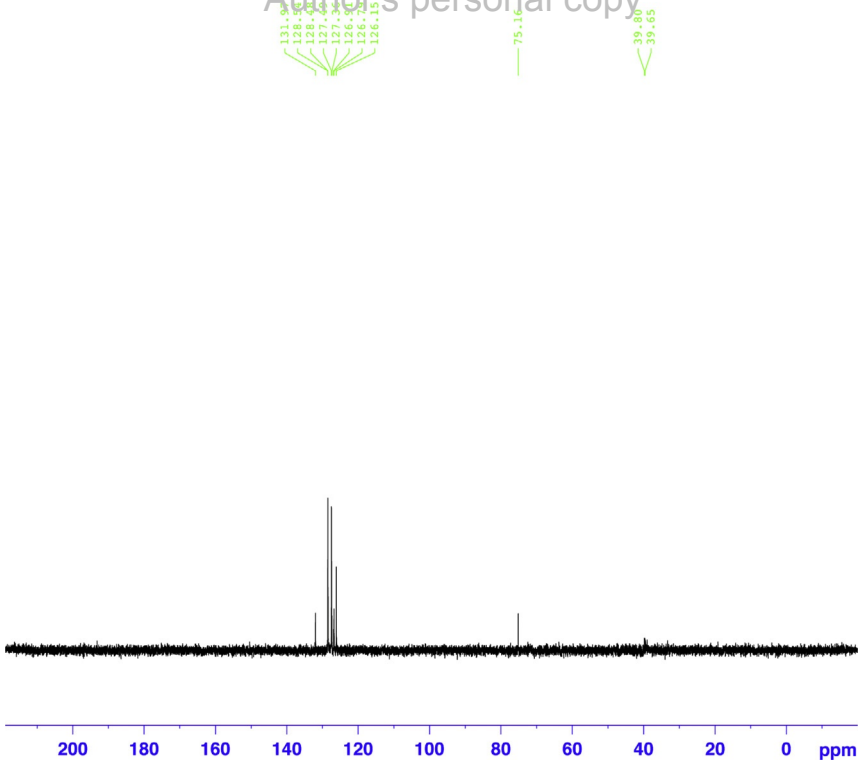


Figure 16 The DEPT 90-1 ^{13}C NMR spectrum of cinnarizine in DMSO-d_6.

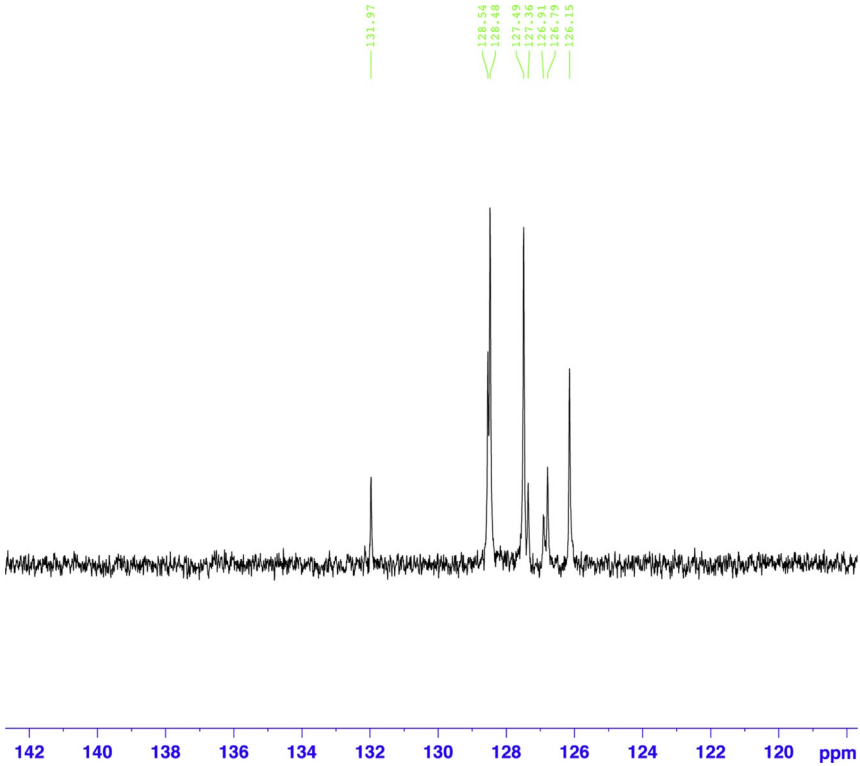


Figure 17 Expanded DEPT 90-2 ^{13}C NMR spectrum of cinnarizine in DMSO-d_6.

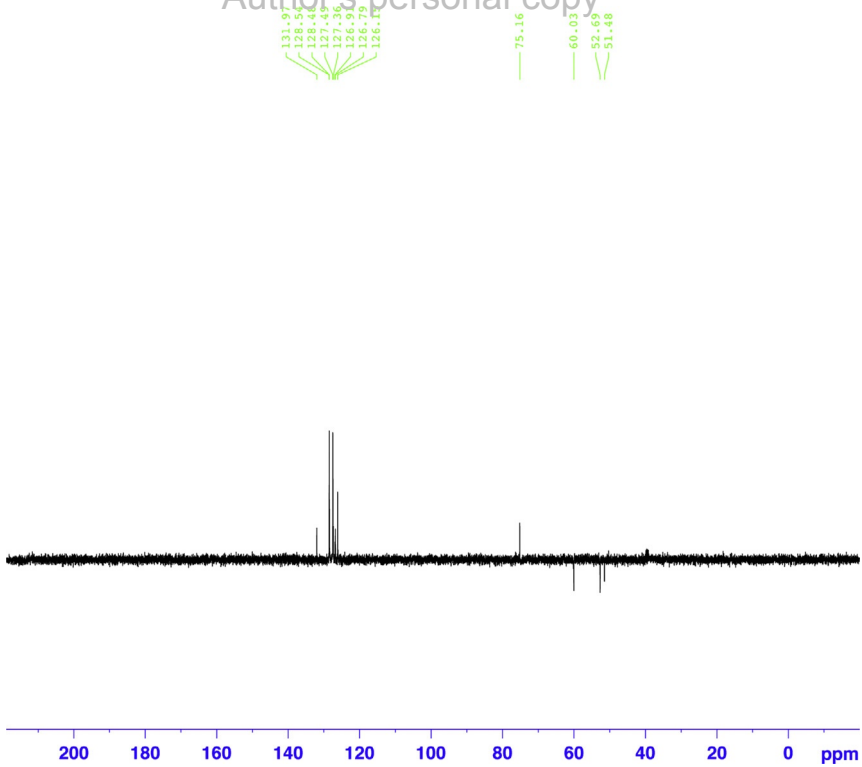


Figure 18 The DEPT 135-1 ^{13}C NMR spectrum of cinnarizine in DMSO-d_6.

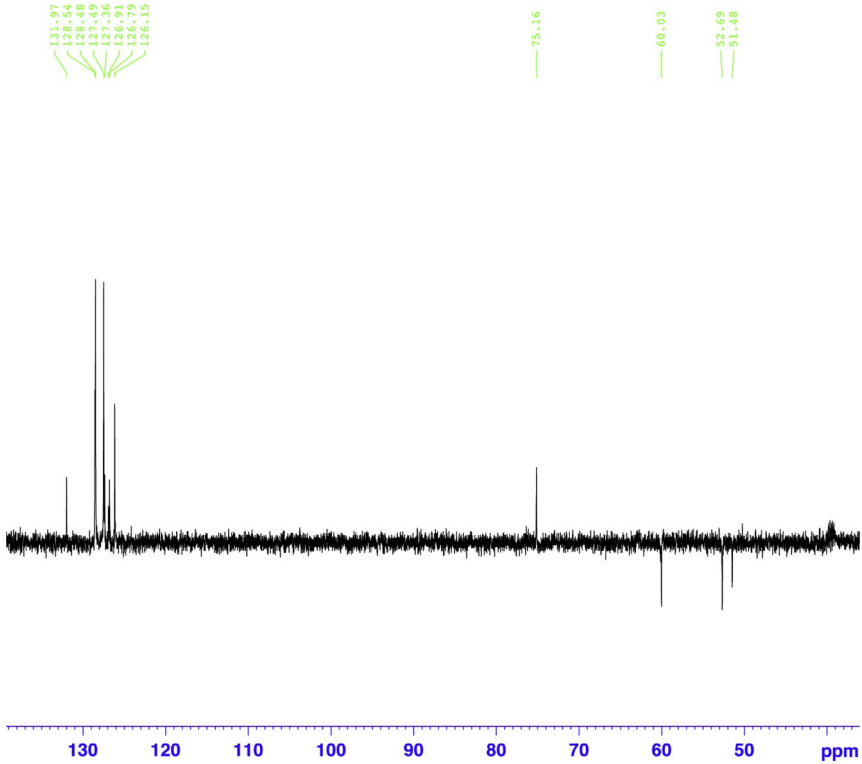
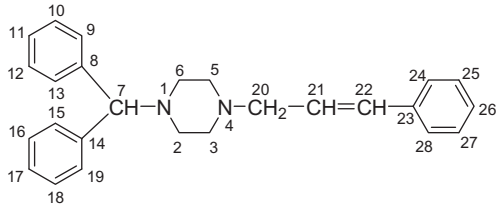


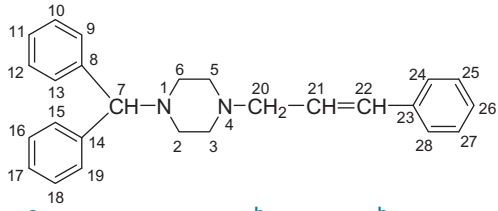
Figure 19 Expanded DEPT 135-2 ^{13}C NMR spectrum of cinnarizine in DMSO-d_6.

Table 4 ^{13}C NMR (δ ppm) Assignments of the Resonance Bands in Cinnarizine



Chemical Shift (δ ppm, Relative to TMS)	Assignments (Carbon Number)
51.50	C-2 and C-6
52.7	C-3 and C-5
60.0	C-20
75.2	C-7
126.1	C-11 and C-17
126.8	C-25 and C-27
126.9	C-26
127.4	C-21
127.5	C-9/C-13, C-15/C-19
128.47	C-10/C-12 and C-16/C-18
128.53	C-24/C-28
132.0	C-22
136.6	C-23
142.9	C-8 and C-14

Table 5 NMR Correlation of Cinnarizine



No.	^{13}C (δ)	^{1}H (δH)[a]	DEPT 90[b]	DEPT 135[b]	COSY	HMBC
1.	–	–	–	–	–	–
2.	51.5	2.33 (2H, m)	–	2	–	–
3.	52.7	2.44 (2H, m)	–	2	–	H-20(^{3}J)
4.	–	–	–	–	–	–

Table 5 NMR Correlation of Cinnarizine—cont'd

No.	^{13}C (δ)	^{1}H (δH)	DEPT 90	DEPT 135	COSY	HMBC
5.	52.7	2.44 (2H, m)	–	2	–	H-20(^{3}J)
6.	51.5	2.33 (2H, m)	–	2	–	–
7.	75.2	4.25 (1H, s)	1	1	–	–
8.	142.9	–	0	0	–	H-7(^{2}J), H-9(^{2}J), H-13(^{2}J)
9.	127.5	7.22–7.29 (1H, m)	1	1	–	H-7(^{3}J), H-10
10.	128.47	7.31–7.42 (1H, m)	1	1	–	H-9
11.	126.1	7.17–7.18 (1H, m)	1	1	–	–
12.	128.47	7.31–7.42 (1H, m)	1	1	–	H-13
13.	127.5	7.22–7.29 (1H, m)	1	1	–	H-7(^{3}J), H-12
14.	142.9	–	–	–	–	H-7(^{2}J), H-15(^{2}J), H-19(^{2}J)
15.	127.5	7.22–7.29 (1H, m)	1	1	–	H-7(^{3}J), H-16
16.	128.47	7.31–7.42 (1H, m)	1	1	–	H-15(^{2}J)
17.	126.1	7.17–7.18 (1H, m)	1	1	–	–
18.	128.47	7.31–7.42 (1H, m)	1	1	–	H-19(^{2}J)
19.	127.5	7.22–7.29 (1H, m)	1	1	–	H-7(^{3}J), H-18(^{2}J)
20.	60	3.08 (2H, d, J=5.5 Hz)	–	2	H-21	–
21.	127.4	6.29 (1H, m)	1	1	H-20, H-22	H-20(^{2}J), H-22(^{2}J)
22.	132	6.51 (1H, d, J=16 Hz)	1	1	H-21	H-20 (^{3}J)
23.	136.6	–	–	–	–	H-25(^{3}J)/H-27(^{3}J)
24.	128.53	7.31–7.42 (1H, m)	1	1	–	–
25.	126.8	7.22–7.29 (1H, m)	1	1	–	H-26 (^{2}J)
26.	126.9	7.21 (1H, m)	1	1	–	–
27.	126.8	7.22–7.29 (1H, m)	1	1	–	H-26 (^{2}J)
28.	128.53	7.31–7.42 (1H, m)	1	1	–	–

[a]δ ppm in DMSO-d_6, J in Hz, 125 MHz for ^{13}C, 500 MHz for ^{1}H.
[b]DEPT is the number of attached protons.

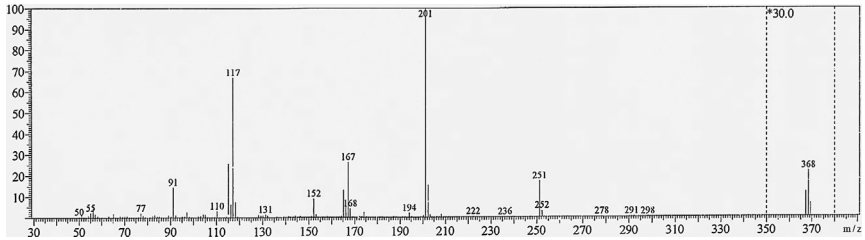
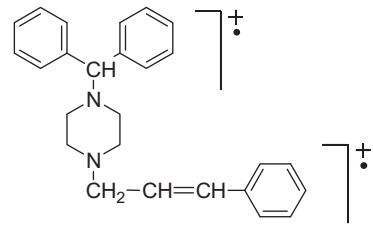
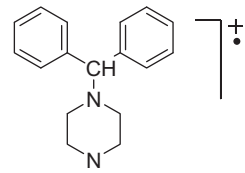
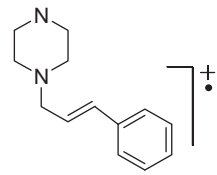
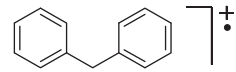
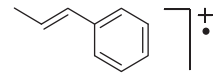
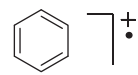


Figure 20 The EI mass spectrum of cinnarizine.

Table 6 Mass Spectral (EI) Assignments in Cinnarizine

		Fragment	
m/z	**Relative Intensity (%)**	**Formula**	**Structure**
368	0.72	$C_{26}H_{28}N_2$	
251	17.11	$C_{17}H_{19}N_2$	
201	100	$C_{13}H_{17}N_2$	
167	26.35	$C_{13}H_{11}$	
117	66.94	C_9H_9	
91	14.50	C_7H_7	
77	2.28	C_6H_5	

4. METHODS OF ANALYSIS

4.1 Compendial Methods

4.1.1 British Pharmacopoeial Methods [9]

Cinnarizine contains not less than 99% and not more than the equivalent of 101% of (*E*)-1-(diphenylmethyl)-4-(3-phenyl-prop-2-enyl)piperazine, calculated with reference to the dried substance.

4.1.1.1 Identification

Test 1. When cinnarizine is tested according to the general method (2.2.14), the melting point of cinnarizine is in the range 118–122 °C.

Test 2. According to the general method (2.2.24), examine cinnarizine by infrared absorption spectrophotometry, comparing with the spectrum obtained with *cinnarizine CRS*. Examine the substance as discs prepared using *potassium bromide R*.

Test 3. According to the general method (2.2.27), examine by thin-layer chromatography using a suitable octadecylsilyl silica gel as the coating substance.

Test solution. Dissolve 10 mg of cinnarizine in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *cinnarizine CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Reference solution (b). Dissolve 10 mg of *flunarizine dihydrochloride CRS* in *methanol R* and dilute to 20 mL with the same solvent.

Apply separately to the plate 5 μL of each solution. Develop over a path of 15 cm using a mixture of 20 volumes of *sodium chloride solution R*, 30 volumes of *methanol R*, and 50 volumes of *acetone R*. Dry the plate in a current of warm air for 15 min and expose to iodine vapor until the spots appear. Examine in daylight. The principal spot in the chromatogram obtained with the test solution is similar in position, color, and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

Test 4. Dissolve 0.2 g of *anhydrous citric acid R* in 10 mL of *acetic anhydride R* in a water bath at 80 °C and maintain the temperature of the water bath at 80 °C for 10 min. Add about 20 mg of cinnarizine. A purple color develops.

4.1.1.2 Tests

Solution S. Dissolve 0.5 g of cinnarizine in *methylene chloride R* and dilute to 20 mL with the same solvent.

Appearance of solution. When the test is carried out as directed in general method (2.2.1), *solution S* is clear and not more intensely colored than reference solution BY_7, as directed in general method (Method II, 2.2.2).

Related substances. Examine by liquid chromatography, as directed in general method (2.2.29).

Test solution. Dissolve 25 mg of cinnarizine in the mobile phase *methanol R* and dilute to 10 mL with the same mobile phase.

Reference solution (a). Dissolve 12 mg of *cinnarizine CRS* and 15 mg of *flunarizine dihydrochloride CRS* in *methanol R* and dilute to 100 mL with the mobile phase.

Reference solution (b). Dilute 1 mL of the test solution to 100 mL with *methanol R*. Dilute 5 mL of this solution with the mobile phase.

The chromatographic procedure may be carried out using:

- a stainless steel column 0.1 m long and 4.0 mm in internal diameter packed with octadecylsilyl silica gel for *chromatography R* (3 μm).
- as mobile phase at a flow rate of 1.5 mL/min a solution of 10 g of *ammonium acetate R* in a mixture of 0.2% v/v solution of *glacial acetic acid R* in *acetonitrile R*.
- as detector, a spectrophotometer set at 230 nm.

Equilibrate the column with the mobile phase at a flow rate of 1.5 mL/min for about 25 min.

Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with 10 μL for reference solution (b) is not less than 50% of the full scale of the recorder.

Inject 10 μL of reference solution (a). When the chromatograms are recorded in the prescribed conditions, the retention times are flunarizine, 11.55 min and cinnarizine, about 11 min. The test is not valid unless the resolution between the peaks corresponding to flunarizine and cinnarizine is not less than 5; if necessary, adjust the condition of the mobile phase.

Inject separately 10 μL of the test solution and 10 μL of reference solution (b). Continue the chromatography for 1.2 times the retention time of the principal peak.

In the chromatogram obtained with the test solution, the area of any peak, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25%); the sum of the areas of all peaks, apart from the principal peak,

is not greater than twice that of the principal peak in the chromatogram obtained with reference solution (b) (0.5%). Disregard any peak due to the solvent and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b).

4.1.1.3 Acidity or Alkalinity

Suspend 0.5 g of cinnarizine in 15 mL of *water R*. Boil for 2 min. Cool and filter. Dilute the filtrate to 20 mL with carbon dioxide-free *water R*. To 10 mL of this solution, add 0.1 mL of *phenolphthalein solution R* and 0.25 mL of 0.01 M *sodium hydroxide*. The solution is pink. To 10 mL of the solution, add 0.1 mL of *methyl red solution R* and 0.25 mL of 0.01 M *hydrochloric acid*. The solution is red.

4.1.1.4 Loss on Drying

When cinnarizine is tested according to the general method (2.2.32), not more than 0.5%, determined with 1 g by drying in an oven *in vacuo* at 60 °C for 4 h.

4.1.1.5 Heavy Metals

When cinnarizine is tested according to the general method (2.4.8), a maximum 20 ppm is obtained.

4.1.1.6 Sulfated Ash

When cinnarizine is tested according to the general method (2.4.14), not more than 0.1%, determined on 1 g.

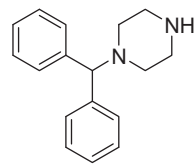
4.1.1.7 Assay

Dissolve 0.15 g of cinnarizine in 50 mL of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with 0.1 M *perchloric acid*, using 0.2 mL of *naphtholbenzein solution R* as indicator. 1 mL of 0.1 M *perchloric acid* is equivalent to 18.43 mg of $C_{26}H_{28}N_2$.

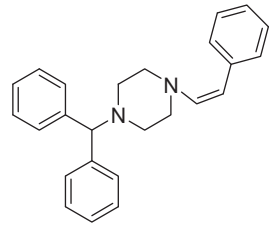
4.1.1.8 Storage

Store in a well-closed container, protected from light.

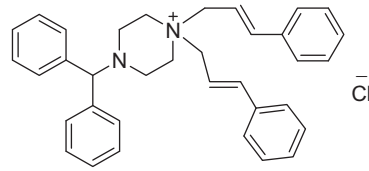
4.1.1.9 Impurities



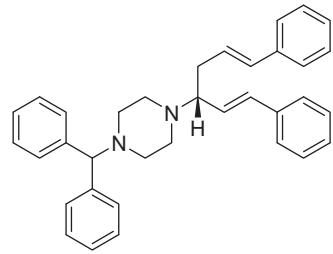
1. 1-(Diphenylmethyl)piperazine



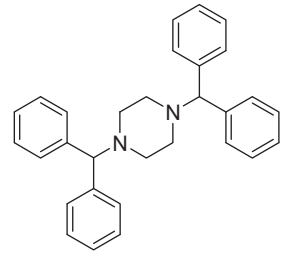
2. (*Z*)-1-(diphenylmethyl)-4-(3-phenyl-prop-2-enyl)piperazine



3. 4-(Diphenylmethyl)-1,1-bis[(*E*)-3-phenyl-prop-2-enyl]piperazine chloride



4. 1-(Diphenylmethyl)-4-[(1*RS*,3*E*)-4-phenyl-1-[(*E*)-2-phenylethenyl] but-3-enyl]piperazine



5. 1,4-Bis(diphenylmethyl)iperazine

4.2 Reported Methods of Analysis

4.2.1 Titrimetric Method

Wu *et al*. [10] titrimetrically determined cinnarizine by a simple and reliable method. Cinnarizine tablets were powdered, treated with tartaric acid and

acetic acid, mixed, and titrated with 0.1 N perchloric acid for cinnarizine determination. Tartaric acid was used to eliminate the interference by magnesium stearate and other basic compounds. Recoveries were ~100%.

Morait and Nedelcu [11] reported the use of gravimetric, titrimetric, and potentiometric methods for the determination of cinnarizine by using the precipitation reactions of cinnarizine with heteropolyacids (silicowolframic acid, phosphowolframic acids, and phosphomolybdic acid). The obtained results allowed the use of these methods to measure cinnarizine in tablets.

Popa *et al.* [12] established two semimicro-analytical methods for the assay of cinnarizine or dipyridamole by the formation of complexes between sodium lauryl sulfate and these pharmaceutical substances by ionic association, with a lower stability than that of lauryl sulfate–Metanil Yellow Complex. Titration with sodium lauryl sulfate 10^{-2} M solution resulted in that the quantified amounts of substance were about 25 mg; thus, the newly established methods may be used for the analysis of tablets containing cinnarizine and dipyridamole.

4.2.2 Spectrophotometric Methods

4.2.2.1 Ultraviolet Spectrometry

Hanmin and Xiuquan [13] reported the determination of cinnarizine in tablets by ultraviolet spectrophotometry based on the measurement of absorbance at 250 nm. Standard plots of absorbances and the concentrations of cinnarizine were linear for 5–25 μg/mL of cinnarizine. Recoveries were 93.9–98.9%.

Saleh and Askal [14] described a spectrophotometric method for the determination of cinnarizine in capsules and tablets based on the charge-transfer complex formation between cinnarizine as n-donor and either iodine as δ-acceptor or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as n-acceptor. Ranges for obedience of absorbance at 295 and 460 nm to Beer's law for cinnarizine with iodine and DDQ were 1–6 and 10–8 μg/mL, respectively. Recoveries of cinnarizine were ~100% and standard deviations were 0.72–1.15%.

Abdine *et al.* [15] developed a direct, extraction-free spectrophotometric method for the determination of cinnarizine in pharmaceutical preparations. The method was based on ion-pair formation between cinnarizine and three acidic (sulfonephthalein) dyes, namely bromocresol green, bromocresol purple, and bromocresol blue which induced an instantaneous bathochromic shift of the maximum in the drug spectrum. Conformity to Beer's law enabled the assay of dosage forms of cinnarizine. Compared with

a reference method, the results obtained were of equal accuracy and precision.

Elazazy *et al.* [16] used a simple, rapid, sensitive, and accurate spectrophotometric method for the determination of cinnarizine, famotidine, and metoclopramide hydrochloride in pure form and in pharmaceutical formulations. The spectral method is based on the reaction between dichlorophenol indophenol and the cited drugs to give bluish violet radical ions exhibiting maximum absorption at 650, 642, and 654 nm for cinnarizine, famotidine, and metoclopramide, respectively, with molar absorptivities 2.421×10^3, 4.313×10^3, and 2.112×10^4 L/mol/cm for cinnarizine, famotidine, and metoclopramide, respectively, and Sandell's sensitivities 6.569×10^{-3}, 1.278×10^{-3}, and 6.646×10^{-3} μg/cm^2.

Devagondanahalli *et al.* [17] described two simple, rapid, and sensitive extractive spectrophotometric methods for the assay of cinnarizine in pure and pharmaceutical formulations. The spectrophotometric methods depend on the formation of chloroform-soluble ion-association complexes of cinnarizine with thymol blue (TB) and with cresol red in sodium acetate–acetic acid buffer of pH 3.6 for TB and in potassium chloride–hydrochloric acid buffer at pH 1.6 for cinnarizine with absorption maxima at 405 and 403 nm for TB and cinnarizine, respectively. Reaction conditions were optimized to obtain the maximum color intensity. The systems obeyed Beer's law in the range of 0.6–15.8 and 0.8–16.6 μg/mL for TB and cinnarizine, respectively. Various analytical parameters have been evaluated and the results have been validated by statistical data.

Tarkase *et al.* [18] reported the development and validation of spectrophotometric method for simultaneous estimation of cinnarizine and domperidone maleate in pure and tablet dosage form. The spectral method depends on simultaneous equation method at two selected wavelength 254 and 284 nm, respectively, and also on absorbance ratio method at two selected wavelengths 274 nm (isoabsorptive point) and 254 nm (λ_{max} of cinnarizine). The linearity was obtained in the concentration range of 5–20 and 5–20 μg/mL for cinnarizine and domperidone maleate, respectively. These methods are accurate, precise, reproducible, and economical, and the results have been validated statistically and by recovery studies.

Abdelrahman [19] described a simultaneous determination of cinnarizine and domperidone in a binary mixture by using area under the curve and dual wavelength spectrophotometric methods. In area under the curve method, mixture solutions in the wavelength ranges 241–258 and 280–292 nm were

selected for the determination of cinnarizine and domperidone, and by applying Cramer's rule the concentration of each drug was obtained. In dual wavelength method, two wavelengths were selected for each drug in a way so that the difference in absorbance is zero for another drug. Domperidone shows equal absorbance at 240.2 and 273.2 nm, where the differences in absorbance were measured for the determination of cinnarizine. Similarly, differences in absorbance at 230.8 and 239.2 nm were measured for determination of domperidone. The spectral methods were applied for the determination of cinnarizine and domperidone over the concentration ranges of 2–20 and 2–22 μg/mL, respectively. Both methods were found to be simple, accurate, sensitive, precise, and inexpensive which could be used in routine and quality control analysis of the cited drugs in pharmaceutical formulations containing them.

Issa *et al.* [20] reported the determination of cinnarizine in pure and in its pharmaceutical dosage forms by spectrophotometric methods carried out to investigate the charge-transfer complex formation between cinnarizine and dipicrylamine (DPA) or 2,6-dinitrophenol (DNP). The colored products were quantified spectrophotometrically at 430 and 440 nm for cinnarizine complexes with DPA in a mixture of 15% dioxane in dichloroethane and 15% ethyl acetate in chloroform, respectively. On the other hand, cinnarizine complexes formed with DNP in acetonitrile and in a mixture of 30% dichloroethane in ethyl alcohol were quantified at 460 and 430 nm, respectively. Beer's law was obeyed in the concentration range of 1–36.8 μg/mL. These methods utilize a single-step reaction and have the advantages of being simple, accurate, sensitive, rapid, and suitable for routine analysis in control laboratories.

4.2.2.2 Spectrofluorimetric Method

Walash *et al.* [21] suggested the use of second-derivative synchronous fluorimetric method for the determination of cinnarizine and domperidone in different pharmaceutical formulations. The fluorimetric method is based upon measurement of the native fluorescence of these drugs at λ_{max} 315 and 324 nm for cinnarizine and domperidone, respectively, after excitation at 280 nm. The synchronous fluorescence spectra of cinnarizine with domperidone were recorded using the optimum $\Delta\lambda$ 80 nm in aqueous methanol (50% v/v). The produced fluorescence-concentration plots were rectilinear obeying Beer's law in the concentration range of 0.1–1.3 and 0.1–3 μg/mL for cinnarizine and domperidone, respectively, with lower detection limits of 0.017 and 5.77×10^{-3} μg/mL and quantification limits of 0.058 and

0.02 μg/mL for cinnarizine and domperidone, respectively. This simple, rapid, and highly sensitive method was successfully applied for the determination of cinnarizine in biological fluids.

4.2.2.3 Chemiluminescence Method

Townsend *et al.* [22] reported a flow-injection chemiluminescence method for the determination of cinnarizine by using the chemiluminescence of permanganate system in the presence of polyphosphoric acid, ethanol, and Tween 60. Five hundred-microliter samples were injected and the sample throughput was 130 h^{-1}. Preliminary experiments identified Tween 60 as the surfactant of choice, improving the detection limit of cinnarizine system 20-fold. Optimum chemiluminescence signals were obtained using 7.5×10^{-4} mol/L potassium permanganate in 0.02 mol/L polyphosphoric acid as the oxidant stream and a carrier stream of 10% (v/v) of ethanol in aqueous 1.5×10^{-3} mol/L Tween 60 with a total flow rate of 7.6 mL/min. The calibration curve was linear from 0.5 to 6 μg/mL with recoveries of 98.4–100.2%.

4.2.3 Voltammetric Methods

El-Sayed *et al.* [23] studied the voltammetric behavior and determination of cinnarizine in pharmaceutical formulations and serum. Cinnarizine was reduced by cyclic linear sweep adsorptive voltammetric method at glassy carbon electrode in Britton–Robinson buffers over the pH range 2.5–11.5. A well-defined adsorption-controlled cathodic peak was obtained at pH 2.5. By cathodic adsorptive linear sweep voltammetry, a linear calibration plot was obtained in the concentration range of 2×10^{-7} to 5×10^{-6} mol/L with detection limit of 9×10^{-9} mol/L. The method is fast, simple, and accurate and has been successfully applied for the determination of cinnarizine in commercial formulations, showing mean recovery and relative standard deviation of 100.24% and 1.46, respectively.

Hegde *et al.* [24] investigated the voltammetric oxidation of cinnarizine in pH 2.5 Britton–Robinson buffer. An irreversible oxidation peak at about 1.2 V at a multi-walled carbon nanotube-modified glassy carbon electrode was obtained. The electrocatalytic behavior was further exploited as a sensitive detection scheme for the determination of cinnarizine by differential pulse voltammetry. Under optimized conditions, the concentration range and detection limit were 9×10^{-8} to 6×10^{-6} and 2.58×10^{-9} M, respectively, for cinnarizine. This method offered the advantage of accuracy, simplicity, and was successfully applied for the determination of cinnarizine in pharmaceutical samples.

4.2.4 Polarographic Method

Nin'o [25] described a polarographic method for the determination of cinnarizine by using a dropping mercury electrode. Cinnarizine tablets were treated with ethanol and then filtered. Ammonium chloride (0.1 M) in 50% ethanol was added to the filtrate and the solution was measured. The method was sensitive to 0.37 mg/mL.

4.2.5 Chromatographic Methods

4.2.5.1 Thin-Layer Chromatography

Clarke [2] recommended the following three thin-layer chromatographic systems:

System 1

Plates: Silica gel G, 250 μm thick, dipped in, or sprayed with, 0.1 M potassium hydroxide in methanol, and dried.

Mobile phase: Methanol:strong ammonia solution (100:1.5).

Reference compounds: Diazepam $R_F = 75$, chlorprothixene $R_F = 56$, and codeine $R_F = 33$, $R_F = 76$ [26].

System 2

Plates: Use the same plates as system 1 with which it may be used because of the low correlation of R_F values.

Mobile phase: Cyclohexane:toluene:diethylamine (75:15:10).

Reference compounds: Dipipanone $R_F = 66$, pethidine $R_F = 37$, desipramine $R_F = 20$, and codeine $R_F = 06$, $R_F = 51$ [26].

System 3

Plates: This system uses the same plates as systems 1 and 2 with which it may be used because of the low correlation of R_F values.

Mobile phase: Chloroform:methanol (90:10).

Reference compounds: Meclozine $R_F = 79$, caffeine $R_F = 58$, dipipanone $R_F = 33$, and desipramine $R_F = 11$, $R_F = 78$ (acidified iodoplatinate solution, positive) [26].

Hassan *et al.* [27] reported the use of an accurate method of thin-layer densitometry for quantification of cinnarizine in dosage forms in the presence of its photodegradation products and metabolites in serum. The thin-layer chromatography mobile phases consisted of benzene:methanol:formic acid (80:17:3) for the resolution of cinnarizine from the associated substances. The samples were applied to precoated silica gel F_{254} plates (20 × 20 cm) and slid into the tank which contained the mobile phase. Visualization of the spots was possible under ultraviolet light and scanning densitometry at 250 nm allowed quantitation. The drug was well separated from the other

related substances and was determined by comparison with standards. Calibration graphs were linear from 10^{-3} to 10^{-6} M of the drug. The lower detection limits were 16 μL^{-1} of cinnarizine with standard deviation of 1.3% and an average recovery of 98.6%.

Bagade *et al.* [28] described a simple high-performance thin-layer chromatographic method for simultaneous estimation of cinnarizine and domperidone in tablet dosage form. It was performed on silica gel 60 GF_{254} thin-layer chromatographic plates using mobile phase comprising of methanol: toluene:ethyl acetate:glacial acetic acid in the ratio of 2:9:0.5:0.5, and the detection was carried out at 216 nm showing R_F value 0.61 for cinnarizine and 0.16 for domperidone. The calibration curve response was observed between 5–14 g for cinnarizine and 4–11 g for domperidone by height and by area. The percentage of drug estimated from cinnarizine and domperidone for marketed formulation was found to be 99.95, 99.82 by height and 100.85, 100.08 by area, respectively. The recovery of drugs was carried out by standard addition method and was found to be 100.13 and 100.18 for cinnarizine and 100.06 and 100.72 for domperidone.

4.2.5.2 Gas Chromatography

Clarke recommended the following gas chromatographic system for the separation of cinnarizine [2].

Column: 2.5% SE-30 on 80–100 mesh Chromosorb G (acid washed and dimethyldichlorosilane-treated), 2 m × 4 mm internal diameter glass column. It is essential that the support is fully activated.

Carrier gas: Nitrogen at 45 mL/min.

Reference compounds: *n*-Alkanes with an even number of carbon atoms.

Retention indices: RI 3065 [29].

Akada *et al.* [30] applied gas chromatography for the determination of cinnarizine in plasma by using an alkali flame ionization detector. The detection limit and determination were, respectively, 0.1 and 0.2 ng/mL. The recovery of cinnarizine in plasma was 104.1%.

Woestenborghs *et al.* [31] developed a sensitive gas chromatographic method for the determination of cinnarizine and flunarizine in plasma, urine, and milk samples from man and animals. The drugs and their internal standard were extracted from the biological samples at alkaline pH, back-extracted into sulfuric acid, and re-extracted into the organic phase (heptane-isoamyl alcohol). The analyses were carried out by gas chromatography using a nitrogen-selective thermionic specific detector. The detection limit was 0.5 ng/mL of biological fluid and extraction recoveries were 87–94%.

Xitian *et al.* [32] used a highly sensitive gas chromatographic method for direct quantitative determination of cinnarizine in tablets. The conditions of determination were FID detector at 280 °C, OV-101 (12 m × 0.25 mm), and fused-silica capillary column, and carbamazepine was used as an internal standard. The temperature was programmed from 200 to 275 °C at 40 °C/min. The response was linear between concentrations 1 and 1.2 mg/mL. The average recovery was 99.98% and the coefficient of variation was 0.92.

4.2.5.3 Gas Chromatography-Mass Spectrometric Method

Maurer and Pfleger [33] described an automated screening procedure using gas chromatography-mass spectrometry (GC-MS) for identification of cinnarizine and other drugs after their extraction from biological sample. This novel analytical procedure has been developed, using computerized GC-MS to detect ethylenediamine and piperazine antihistamines and their metabolites in urine which was used because the drug concentrations are higher in urine than in plasma. After acid hydrolysis and acetylation of the sample, the acetylated extract was analyzed by computerized GC-MS. By using ion chromatography with the selective ions m/z 58, 72, 85, 125, 165, 183, 198, and 201, the possible presence of cinnarizine or piperazine antihistamines or their metabolites was indicated. The identity of positive signals in the reconstructed ion chromatogram was then confirmed by a visual for computerized comparison of the stored full mass spectra with the reference spectra. The ion chromatograms, reference mass spectra, and gas chromatographic retention indices (OV-101) were documented.

4.2.5.4 High-Performance Liquid Chromatographic Methods

Nowacka-Krukowska *et al.* [34] used a high-performance liquid chromatographic method for the determination of cinnarizine in plasma. Cinnarizine was extracted from plasma with a mixture of chloroform and *n*-hexane (2:3, v/v) and separated by high-performance liquid chromatography column MicroSpher C_{18} with a fluorescence detector at $\lambda_{ex} = 245$ nm and $\lambda_{em} = 310$ nm. The mobile phase was 0.01 M ammonium dihydrogen phosphate buffer (pH 4.2) containing 0.038% triethylamine and acetonitrile (25:75, v/v). The flow rate was 1 mL/min. The calibration curves were linear over the range 1–100 ng/mL. Recovery was 97%. The intra- and inter-day relative standard deviations were less than 10% and the accuracy of the assay expressed by bias was in the range 0.14–2.37%. The minimum detectable concentration of cinnarizine was determined at 1.25 ng/mL and the lowest limit of quantitation was found to be 1 ng/mL of plasma.

Heda *et al.* [35] established a simple and precise reverse-phase high-pressure liquid chromatographic method for the determination of cinnarizine in pharmaceutical formulation. A sample containing 75 mg of cinnarizine was dissolved in 40 mL of a mixture of ethanol and acetate buffer (pH 5.5) in 1:1 proportion, ultrasonicated for 10 min, and then the volume was made up to 50 mL with the same mixture. The solution was filtered and 20 μg/mL of the filtrate was analyzed by reverse-phase high-pressure liquid chromatography on a column (length × OD × ID = 33 × 8 × 6 mm, 1.5 μm) of MICRA-NPS C_{18} with a mobile phase prepared by mixing acetonitrile, triethylamine buffer (adjusted to pH 4.5 with 10% potassium hydroxide), and tetrahydrofuran in the ratio of 30:66:4, respectively, at a flow rate of 0.5 mL/min. Detection was at 253 nm. The calibration graph was rectilinear for 20–100 μg/mL of cinnarizine. Recovery was within the range of 100 ± 2%. The limit of detection and limit of quantification were found to be 0.0592 and 0.1794 μg/mL, respectively.

4.2.5.5 High-Performance Liquid Chromatography-Mass Spectrometry

Liu *et al.* [36] used a high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) with electrospray ionization (ESI) to separate and simultaneously quantify cinnarizine, sodium ferulate, salicylic acid, and vitamin B, in human plasma. The internal standards used were lomerizine for cinnarizine and vitamin B_1, whereas gemfibrozil was used for sodium ferulate and salicylic acid. The plasma samples were prepared by one-step protein precipitation followed by an isocratic elution with 10 mM ammonium acetate buffer:acetonitrile (35:65, v/v) at pH 5 on an Agilent Zorbax SB-CN column (150 mm × 2 mm ID, 5 μm). The precursor and product ions of cinnarizine and the other drugs were monitored on a triple quadruple mass spectrometer, operating in the selected reaction monitoring mode with polarity switch, in the negative-ion mode for sodium ferulate, salicylic acid, and gemfibrozil, and in the positive-ion mode for cinnarizine, vitamin B_1, and lomerizine. The results showed that the calibration curves were linear in the range from 2 to 500 ng/mL for cinnarizine, $r = 0.9992$ with recoveries ranging from 98.4 to 100.33%, whereas for sodium ferulate in the range of 1.5–1000 μg/mL, $r = 0.9991$ with recoveries 99.24–88.83%, while salicylic acid in the range of 20–5000 μg/mL, $r = 0.9988$ showed recoveries in the range of 93.2–82.45% and vitamin B_1 in the range of 1–30 ng/mL, $r = 0.9928$ with recoveries 94.61–86.59%.

Van De Steene and Lambert [37] developed a quantitative liquid chromatography-electrospray tandem mass spectrometric (ESI)-MS/MS method for the simultaneous analysis of cinnarizine and other pharmaceuticals in environmental waters. Sample preparation consisted of solid-phase extraction on a Speedisk phenyl and an NH_2 solid-phase extraction tube for sample clean-up. Chromatography was performed on a pentafluorophenyl column in a total run time of 24 min. Standard addition was the only method to perform accurate quantification due to different matrix effects measured in different surface water samples. Limits of detection and determination were in the range of <0.05–1 and 0.05–10 ng/L, respectively. Recoveries were in the range of 60–100%. The method was successfully applied to influent, effluent, and surface water samples. Also, removal percentage of these drugs could be estimated.

4.2.5.6 Capillary Electrophoresis

Abdelal *et al.* [38] described a validated simultaneous determination of cinnarizine and domperidone and cinnarizine and nicergoline in their coformulated tablets by capillary electrophoresis which was performed using a CAPI-3100 CE system equipped with a multiwavelength ultraviolet–visible detector and an automated sampler. An uncoated fused-silica capillary (40 × 50 μm) was used for the separation. Optimization of capillary electrophoretic method was established by using a running buffer, methanol–acetate buffer (pH 3, 10 mM) (80:20 v/v) for cinnarizine and nicergoline at wavelength 227 nm. The voltage applied was 20 kV and the hydrodynamic injection was performed at a height of 25 mm for 30 s. Under these conditions, the calibration graphs were linear over the ranges 0.25–20 and 0.375–15 μg/mL for cinnarizine and domperidone, whereas they were linear over the ranges 0.25–25 and 0.4–10 μg/mL with detection limits at 0.072 and 0.116 μg/mL for cinnarizine and nicergoline. The relative standard deviation was ≤2.34% ($n = 3$).

5. BIOLOGICAL ANALYSIS

Siegler *et al.* [39] described a human bioassay for cinnarizine. The assays were carried out by a double-blind method with placebo in groups of 30–60 patients. The doses were determined at which the antihistamines produced a beneficial effect in 50% and toxic effects in 25% of the patients which were 12 and 25 mg for cinnarizine.

A comparative bioassay of vasoactive drug, cinnarizine, by using isolated perfused arteries was developed by Van Nueten [40]. A simple and reliable assay for cinnarizine is described by using potassium chloride-depolarized central artery preparations from the rabbit ear and saphenous artery preparation from the hind leg. Cinnarizine was assayed for potency, rate of onset, and duration of action (inhibiting potassium chloride-induced vasoconstriction).

Dhall *et al.* [41] assessed the vasopressor activity of human amniotic fluid of 46 primigravidas during the third trimester of pregnancy. The samples of amniotic fluid showing vasopressor activity were lyophilized and subjected to gel filtration using Sephadex G-100. The various fractions thus obtained were monitored at 280 nm and the pressor activity was re-estimated. It was observed that most of the amniotic fluid of the toxemic patients was capable of causing contraction of the rat colon as well as a significant rise in the systolic blood pressure of the intact rat. Furthermore, this activity was found to be heat-labile and was completely blocked by cinnarizine.

Ogata *et al.* [42] evaluated beagle dogs as an animal model for bioavailability testing of cinnarizine capsules. The bioavailability of cinnarizine 25 mg from two commercial capsules were determined in beagle dogs and compared with that previously found in humans given the same preparations. The gastric acidity did not affect the bioavailability of cinnarizine in beagle dogs, although the human study had shown a distinct effect of gastric acidity on the bioavailability. Consequently, beagle dogs cannot be used as an animal model for predicting the human bioavailability of cinnarizine, since they do not affect the gastric acidity dependency that is observed in humans.

Also, Hassan *et al.* [27] developed a new high-performance (HPLC) and thin-layer densitometric (TLC) methods for quantification of cinnarizine in dosage forms in the presence of its photodegradation products, related substances, and in the presence of its metabolites in serum. The methods applied provided assessment of cinnarizine purity, bioavailability, stability, and tablet dissolution rate.

Konieczna *et al.* [43] studied the relationships between experimental and computational descriptors of antihistamine drugs, including cinnarizine by using principal component analysis (PCA). A matrix of 18×49 data, including high-performance chromatography and ultraviolet and infrared spectroscopic data, together with molecular modeling studies, was evaluated by the PCA method. The obtained clusters of drugs were consistent with the drugs' chemical structure classification, and hence, it may potentially help limit the number of biological assays in the search of new drugs.

6. STABILITY

Tokumura *et al.* [44] investigated the stability of cinnarizine in aqueous solution at various pH values and temperatures. The degradation of cinnarizine was observed as a pseudo-first-order reaction. By determining the degradation rate of cinnarizine at various pH values, it was found that the degradation rate of cinnarizine increased with decreasing pH within the range of 3–1. The rate of degradation remained unchanged below pH 1.2 and cinnarizine was stable above pH 3. The rate constant (k) at 60 °C was found to be $1.85 \times 10^{-5}/\text{min}^{-1}$ which is 100 times less than that at 90 °C. Consequently, the results indicate that the degradation rate of cinnarizine increases with increasing temperature.

Shi *et al.* [45] studied the stability, formulation, and degradation kinetics of intravenous cinnarizine lipid emulsion. Cinnarizine was loaded in the lipid emulsion to develop an intravenous formulation with good physical and chemical stability. The lipid emulsion was prepared by using high-pressure homogenization. The factors influencing the stability of cinnarizine lipid emulsion, such as different loading methods, pH, temperature, sterilization methods, and time, were monitored by high-performance liquid chromatography. The degradation of cinnarizine in aqueous solution and lipid emulsion both followed apparent first-order kinetics. Also, a possible degradation mechanism was postulated by the bell-shaped pH-rate profile of cinnarizine. It was found that localization of the drug in the interfacial lecithin layer significantly improved the chemical stability of cinnarizine. The activation energy of cinnarizine in lipid emulsion was calculated to be 51.27 kJ/mol which was similar to that in aqueous solution. Furthermore, the shelf-life of cinnarizine in lipid emulsion was estimated to be 1471.6 days at 4 °C, which is much longer compared with 19.8 days in aqueous solution.

Shahba *et al.* [46] assessed the stability of cinnarizine in self-emulsifying drug delivery systems. The chemical and physical stability of cinnarizine was evaluated within self-emulsifying drug delivery systems. The selected formulations were enrolled into both accelerated and long-term stability studies up to 6 and 12 months. The chemical stability of the formulations was assessed periodically based on the intact cinnarizine level, while the physical stability was evaluated based on the physical appearance and color change patterns of the formulations. The accelerated stability study revealed significant cinnarizine degradation within 6 months of storage. On the other hand, the long-term stability study showed no significant degradation or

change of color of cinnarizine within the formulations containing 100% saturated medium chain glycerides (as oil component). However, the formulations containing 50% unsaturated long chain fatty acids showed considerable drug degradation as well as significant discoloration. Thus, the formulations containing 100% saturated medium chain glycerides provide excellent chemical and physical stability pattern and have the potential to provide a stable dosage form of cinnarizine.

7. PHARMACOKINETICS, METABOLISM, AND EXCRETION

Castañeda-Hernández *et al.* [47] studied the pharmacokinetics of cinnarizine after single and repetitive dosing in healthy volunteers. Blood samples were drawn from six young healthy male subjects after receiving a 75-mg cinnarizine tablet for 72 h. Cinnarizine plasma levels were determined by gas chromatography. Then, after a 2-week washout period, five of these subjects received 75-mg tablets for 15 days. Blood samples were drawn for 12 h and cinnarizine plasma levels were measured. The results indicated that cinnarizine accumulates with repetitive dosing due to its pharmacokinetic properties.

Kariya *et al.* [48] investigated the potentialities of cinnarizine and its fluorine derivative flunarizine to induce Parkinsonism as an adverse effect. The study was evaluated pharmacokinetically and pharmacodynamically in rats after giving them a daily dose of 20 μmol/kg of cinnarizine or flunarizine for 1, 5, 10, 15, and 30 days. The active metabolites of their cinnamyl moiety in the plasma and striatum were determined 24 h after the final dose. The results indicate that on the basis of the equimolar dosing performed, flunarizine is a more potent inducer of Parkinsonism than cinnarizine and that their active metabolites contribute to the development of Parkinsonism during chronic medication with cinnarizine and flunarizine.

Tokumura *et al.* [49] studied the improvement of oral bioavailability of flurbiprofen from flurbiprofen/β-cyclodextrin inclusion complex by the action of cinnarizine. Flurbiprofen and flurbiprofen/β-cyclodextrin were administered to fasted rats at a dose of 20 mg/kg as flurbiprofen. After 30 min of drug administration, 0.17 mg/kg of cinnarizine dissolved in pH 4 buffer solution was administered to the rats. Blood samples were taken from the rats and the concentrations of flurbiprofen in plasma samples were determined by high-performance liquid chromatography. It was found that cinnarizine had no effect on plasma concentrations of flurbiprofen after oral administration of the drug. On the other hand, the mean plasma levels after

oral administration of flurbiprofen/β-cyclodextrin with cinnarizine were larger than those of flurbiprofen and those of flurbiprofen/β-cyclodextrin. Consequently, this result is considered to be caused by the action of cinnarizine as a competing agent *in vivo* which was supported by the decrease in solubility of flurbiprofen in β-cyclodextrin upon the addition of cinnarizine.

Shi *et al.* [50] assessed the potential of cinnarizine loaded in lipid emulsion to modify the pharmacokinetics, tissue distribution, and safety of the drug. The cinnarizine-loaded emulsion was prepared by high-pressure homogenization. The pharmacokinetics and tissue distributions of cinnarizine lipid emulsion were evaluated by comparing with the solution form after intravenous administration to rats at a dose of 2 mg/kg. The cinnarizine lipid emulsion showed significantly higher area under the concentration/time curve and lower clearance and distribution volume than those of a solution form. This helped cinnarizine to reach higher level in vessel and circulate in the blood stream for a longer time, resulting in better therapeutic effect. While the tissue distribution showed a significantly lower uptake of cinnarizine lipid emulsion in lung and brain, indicating the advantage of the emulsion over the solution form in reducing drug precipitation *in vivo* and toxicity in the central nervous system. In addition, the intravenous safety investigation proved that cinnarizine lipid emulsion was safe as an intravenous injection.

Soudijn and van Wijngaarden [51] studied the metabolism and excretion of ^{14}C cinnarizine in male rats after a single intraperitoneal administration at a dose of 20 mg/kg. Urine and feces were collected separately once a day for 3 weeks. After administration of ^{14}C cinnarizine, the excretion of radioactive material was maximal during the first 5 days. After 10 days, less than 1% was excreted and after 3 weeks residual radioactivity was less than 0.1% of the administered dose and amounted to 5 μg per rat, mainly concentrated in the liver, gastrointestinal tract, and carcass. It was found that the major metabolite in urine was benzhydrol, mainly in the conjugated form, while the main metabolites in the feces were benzhydrylpiperazine and benzophenone, with small amounts of unaltered cinnarizine. Thus, N-dealkylation was the major pathway of metabolism of cinnarizine in rats. About one-third of the radioactive metabolites were excreted in the urine and two-thirds in the feces, predominantly during the first 5 days after administration of the drug.

Kariya *et al.* [52] investigated the oxidative metabolism of cinnarizine in rat liver by the microsomal monooxygenase system, including P450 to

1-(diphenylmethyl)piperazine, 1-(diphenylmethyl)-4[3-(4′-hydroxyphenyl)-2-propenyl]piperazine, benzophenone, and 1-[(4′-hydroxyphenyl)-phenylmethyl]-4-(3-phenyl-2-propenyl)piperazine. The reactions required NADPH and were inhibited by carbon monoxide and SKF 525-A. The results indicate that cinnarizine is oxidized by cytochrome P450 and that the formation of 1-(diphenylmethyl)-4-[3-(4-hydroxyphenyl)-2-propenyl] piperazine is related to debrisoquine/spartein-type polymorphic drug oxidation.

8. PHARMACOLOGY

Cinnarizine is a piperazine derivative with antihistaminic and calcium channel-blocking activities. It inhibits calcium translocation across the vestibular sensory cells in the ampullae and maintains endolymph flow by preventing constriction of the stria vascularis. Cinnarizine is a potent dilator of the peripheral vessels, with no corresponding calcium-blocking actions in the heart [53].

Elimadi *et al.* [54] investigated the effects of cinnarizine on mitochondrial permeability transition, ATP synthesis, membrane potential, and NAD(P)H oxidation. Cinnarizine was effective in inhibiting the mitochondrial permeability transition induced either by calcium (Ca^{2+}) alone or in the presence of *tert*-butylhydroperoxide. At low concentration of cinnarizine (<50 μM), the protective effect occurred which was accompanied by the inhibition of NAD(P)H oxidation and the restoration of the mitochondrial membrane potential decreased by a high concentration of Ca^{2+} (25 μM). However, at higher concentrations (>50 μM) of cinnarizine and in the absence of both *tert*-butylhydroperoxide and Ca^{2+}, the effects of cinnarizine on the mitochondria were reversed as the mitochondrial permeability transition was generated, mitochondrial NAD(P)H was oxidized, and the membrane potential collapsed. It was found that both effects might be linked to the binding of cinnarizine to mitochondrial hydrophobic sites and the shift from the inhibition to induction of the mitochondrial permeability transition being dependent on the concentration of cinnarizine.

Terland and Flatmark [55] reported that cinnarizine inhibited the MgATP-dependent generation of transmembrane proton electrochemical gradient in chromaffin granule ghosts and thus inhibiting proton pumping and catecholamine uptake in storage vesicles *in vivo*. This mechanism of action may contribute to the drug-induced Parkinsonism observed as a side effect of cinnarizine.

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